Polycomb-like 3 promotes polycomb repressive complex 2 binding to CpG islands and embryonic stem cell self-renewal.

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Public Summary:
Embryonic development requires coordinated changes in gene expression to differentiate specific cell types. Coordinated gene regulation is also important for maintaining tissue homeostasis and preventing cancer. Histone modifications contribute to the control of gene expression by affecting chromatin structure and recruitment of regulatory proteins. Polycomb repressive complex 2 (PRC2) catalyzes the methylation of a lysine residue on histone H3, an early step in gene repression. It remains unclear how PRC2 is recruited to and regulated at many genes. Here, we describe data indicating that Polycomb-like 3 (Pcl3), a protein upregulated in diverse cancers, is a component of PRC2 that promotes PRC2 binding and function at target genes. We also demonstrate that Pcl3 is important for embryonic stem cell self-renewal. These findings indicate that Pcl3 is a critical regulator of gene repression and stem cell self-renewal that acts by controlling PRC2 activity.

Scientific Abstract:
Polycomb repressive complex 2 (PRC2) trimethylates lysine 27 of histone H3 (H3K27me3) to regulate gene expression during diverse biological transitions in development, embryonic stem cell (ESC) differentiation, and cancer. Here, we show that Polycomb-like 3 (Pcl3) is a component of PRC2 that promotes ESC self-renewal. Using mass spectrometry, we identified Pcl3 as a Suz12 binding partner and confirmed Pcl3 interactions with core PRC2 components by co-immunoprecipitation. Knockdown of Pcl3 in ESCs increases spontaneous differentiation, yet does not affect early differentiation decisions as assessed in teratomas and embryoid bodies, indicating that Pcl3 has a specific role in regulating ESC self-renewal. Consistent with Pcl3 promoting PRC2 function, decreasing Pcl3 levels reduces H3K27me3 levels while overexpressing Pcl3 increases H3K27me3 levels. Furthermore, chromatin immunoprecipitation and sequencing (ChIP-seq) reveal that Pcl3 co-localizes with PRC2 core component, Suz12, and depletion of Pcl3 decreases Suz12 binding at over 60% of PRC2 targets. Mutation of conserved residues within the Pcl3 Tudor domain, a domain implicated in recognizing methylated histones, compromises H3K27me3 formation, suggesting that the Tudor domain of Pcl3 is essential for function. We also show that Pcl3 and its paralog, Pcl2, exist in different PRC2 complexes but bind many of the same PRC2 targets, particularly CpG islands regulated by Pcl3. Thus, Pcl3 is a component of PRC2 critical for ESC self-renewal, histone methylation, and recruitment of PRC2 to a subset of its genomic sites.